

PATENT SPECIFICATION

NO DRAWINGS

869.775



Date of Application and filing Complete Specification: Sept. 15, 1959.

No. 31457/59.

Application made in United States of America on Sept. 24, 1958.

Complete Specification Published: June 7, 1961.

Bibliotek
Burr. Ind. Engonom
15 JUL 1961

Index at acceptance:—Classes 2(3), C1C(2: 9: 11F: 11J), C1D(4: 6), C1E(4: 6), C1F(4: 6), C1G(4: 6), C1H(4: 6), C1I(4: 6), C1J(4: 6), C1K(4: 6), C1L(4: 6), C1M(4: 6), C1N(4: 6), C1O(4: 6), C1P(4: 6), C1Q(4: 6), C1R(4: 6), C1S(4: 6), C1T(4: 6), C1U(4: 6), C1V(4: 6), C1W(4: 6), C1X(4: 6), C1Y(4: 6), C1Z(4: 6), C2B(20: 31), C3A12(A4A: B3: B4: C6), C3A14A(3D: 8D), C3C5(A4: C7: E2); and 81(1), B2S.

International Classification:—C07d. A61k.

COMPLETE SPECIFICATION

3-Indolyl Ketones

We, THE UPJOHN COMPANY, a corporation organized and existing under the laws of the state of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a novel process for the preparation of derivatives of heterocyclic compounds and is more particularly concerned with a process for the preparation of ketones of the indole series and with certain novel 3-indolyl ketones produced thereby.

A number of methods have been described previously for the preparation of indolyl ketones. Thus, for example, the preparation of 3-indolyl ketones has been accomplished by treating indole Grignard reagents with acid chlorides [Salway, J. Chem. Soc. 103, 353 (1913)], small yields of the corresponding N-acetylindoles being obtained simultaneously. Borsche and Groth [Ann. 549, 238 (1941)] obtained 2- and 3-acetylindoles by a Friedel-Crafts reaction between acetyl chloride and indole or substituted indoles: where the 2- and 3-positions are occupied, the acetyl group enters the benzene ring. The Hoesch synthesis has been applied by Seka [Ber. 56, 2058 (1923)] to the preparation of indole ketones, 3-indolyl ketones being obtained preferentially. In German Patent 614,326 there is described a process for the preparation of 3-*p*-chlorobenzoyl-1-methyl-2-phenylindole by reacting 1-methyl-2-phenylindole with phosphorus oxychloride and *p*-chlorobenzanilide; the preparation of 3-*p*-chlorobenzoyl-1,2-dimethylindole by reacting 1,2-dimethylindole with *p*-chlorobenzanilide and phosphorus oxychloride is also described. This reaction is not, however, of general applicability. Thus, when the reaction is repeated using acetanilide in place of *p*-chlorobenzanilide and indole in place of 1-

methyl-2-phenylindole and 1,2-dimethylindole, the resulting yield of the expected 3-acetylindole is small. Further, in order to isolate the desired indole ketone from the reaction mixture obtained using the procedure described in the above German Patent, it is necessary to submit the crude reaction product to acid hydrolysis in order to decompose the intermediate phosphorus-containing complex which is formed. The indole ketone so isolated is still in a crude state and requires considerable further treatment in order to free it from impurities.

In accordance with the present invention it has been found that 3-indolyl ketones can be obtained readily and in high yield by the reaction of an indole, which is unsubstituted in the 3-position, with phosphorus oxychloride and a carboxylic acid amide in which at least one, and preferably both, hydrogens on the nitrogen atom of the amide linkage are replaced by a lower-alkyl radical. The carboxylic acids from which the said amides are derived include hydrocarbon carboxylic acids such as saturated and unsaturated aliphatic acids, cycloaliphatic acids and aromatic carboxylic acids. The hydrocarbon carboxylic acids can be substituted by one or more inert radicals i.e., radicals which are inert under the conditions of the process of the invention, such as halo, cyano, nitro, tertiary amino, alkoxy, aralkoxy, aryloxy, alkylmercapto, aralkylmercapto or arylmercapto. The reaction is general in application and is suitable for operation on a large scale. Further, the process of the invention does not suffer from the disadvantages attendant upon the use of the procedure described in German Patent 614,326 discussed above. Thus the process of the present invention is distinguished not only by its general applicability, but as will be more particularly described hereafter, by the ease with which the reaction product can be decomposed to furnish the required indolyl ketone in high yield and state of purity.

[Price 3s. 6d.]

BEST AVAILABLE COPY

Actions Due Date Report

Date of Report: 21.04.2005

```

*****
Action Due   Action Description      Att. AoR      Dkt.No      SN Ctry C R F CV S
-----
23.07.2004   IB 301 Record Copy                CMC          100998      1  WO          P S F
23.03.2005   International Preliminary Exam CMC          100996      1  WO          P S F
23.03.2005   Final date Demand                 CMC          100998      1  WO          P S F
09.04.2005   IPEA FORM 402                     CMC          100992      1  WO          P S F
10.04.2005   Form B1 to AM or AS                CMC          101532      1  US      L      B F
16.04.2005   Form B1 to AM or AS                CMC          101364      1  US      L      B F
23.04.2005   IPEA FORM 402                     CMC          100996      1  WO          P S F
23.04.2005   IPEA FORM 402                     CMC          100998      1  WO          P S F
29.04.2005   IPEA FORM 402                     CMC          100975      1  WO          P S F
30.04.2005   Final date Demand                 CMC          100993      1  WO          P S F
30.04.2005   Final date Demand                 CMC          100997      1  WO          P S F
09.05.2005   Form B2 to AM or AS                CMC          100992      1  WO          P S F
23.05.2005   Form B2 to AM or AS                CMC          100996      1  WO          P S F
23.05.2005   Form B2 to AM or AS                CMC          100998      1  WO          P S F
29.05.2005   Form B2 to AM or AS                CMC          100975      1  WO          P S F
30.05.2005   IPEA FORM 402                     CMC          100993      1  WO          P S F
30.05.2005   IPEA FORM 402                     CMC          100997      1  WO          P S F
30.05.2005   Form 3A to Formalities             CMC          101371      1  US      L      B F
10.06.2005   Form 3A to Formalities             CMC          101532      1  US      L      B F
16.06.2005   Form 3A to Formalities             CMC          101364      1  US      L      B F
20.06.2005   Form 3B to Formalities             CMC          101371      1  US      L      B F
30.06.2005   Form B2 to AM or AS                CMC          100993      1  WO          P S F
30.06.2005   Form B2 to AM or AS                CMC          100997      1  WO          P S F
01.07.2005   Form 3B to Formalities             CMC          101532      1  US      L      B F

```

Actions Due Date Report for EP/US AoR

Date of Report: 21.04.2005

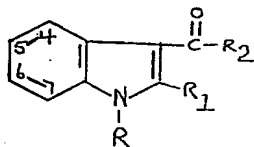
```

*****
Action Due   Action Description      Att. AoR      Dkt.No      SN Ctry C R F CV S
-----
21.02.2005   Info Discl. Statement             PJF CMC          100746      1  US          P S F
21.02.2005   Info Discl. Statement             PJF CMC          100747      1  US          P S F
21.02.2005   Info Discl. Statement             PJF CMC          100811      1  US          P S F
21.02.2005   Info Discl. Statement             PJF CMC          100812      1  US          P S F
21.02.2005   Info Discl. Statement             PJF CMC          100813      1  US          P S F
21.04.2005   Info Discl. Statement             PJF CMC          100746      1  US          P S F
21.04.2005   Info Discl. Statement             PJF CMC          100747      1  US          P S F
21.04.2005   Info Discl. Statement             PJF CMC          100811      1  US          P S F
21.04.2005   Info Discl. Statement             PJF CMC          100812      1  US          P S F
21.04.2005   Info Discl. Statement             PJF CMC          100813      1  US          P S F
21.04.2005   Power of Attorney                 PJF CMC          100811      1  US          P S F
21.04.2005   Power of Attorney                 PJF CMC          100813      1  US          P S F
21.05.2005   File Assignment                   PJF CMC          100811      1  US          P S F
21.05.2005   File Assignment                   PJF CMC          100813      1  US          P S F

```

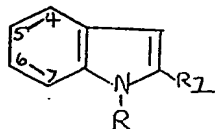
Accordingly, it is an object of the present invention to provide a process for the preparation of 3-indolyl ketones, which process is of general application and can be carried out readily on a commercial scale. It is a further object of the invention to provide certain novel 3-indolyl alkyl ketones which possess valuable pharmacodynamic properties. Other objects of the invention will be apparent to those skilled in the art to which this invention pertains.

While the process of the present invention can be applied to the preparation of 3-indolyl ketones using as starting materials any indole which is unsubstituted in the 3-position, and any mono- or di-lower-alkylamide of a hydrocarbon carboxylic acid, it is particularly applicable to the preparation of 3-indolyl ketones having the general formula



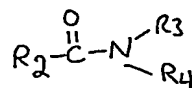
(I)

wherein R represents hydrogen or a lower-alkyl or lower-aralkyl radical, R₁ represents hydrogen or a lower-alkyl, lower-aralkyl, lower-aryl or lower-haloaryl radical, R₂ represents a lower-alkyl, lower-haloalkyl, lower-aralkyl or lower-aryl radical, and the 4-, 5-, 6-, and 7-positions in the benzene nucleus can be substituted by lower-alkyl, lower-aryl, lower-alkoxy, lower-aralkyl, lower-aralkoxy, lower-aryloxy radicals or a halogen. When a compound having the formula (I) above is substituted by one or more benzyloxy groups in the 4-, 5-, 6-, or 7-positions, said benzyloxy group or groups can be converted to the corresponding hydroxy group or groups, for example, by hydrogenolysis according to the procedure described in British Specification No. 744,774. The ketones of the above general formula can be prepared according to the process of the present invention, by reacting an indole having the general formula:



(II)

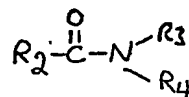
wherein R and R₁ have the significance hereinbefore defined and the 4-, 5-, 6-, and 7-positions in the benzene nucleus can be substituted as hereinbefore described, with phosphorus oxychloride and an amide having the formula



where R₂ has the significance hereinbefore defined, R₃ is hydrogen or a lower-alkyl radical and R₄ represents a lower-alkyl radical.

The term "lower-alkyl radical" as used in this specification is intended to mean an alkyl radical which contains from one to eight carbon atoms such as methyl, ethyl, propyl, butyl, amyl, hexyl, heptyl, octyl and isomeric forms thereof; the term "lower-alkoxy radical" is intended to mean an alkoxy radical which contains from one to eight carbon atoms such as methoxy, ethoxy, propoxy, butoxy, amyloxy, hexyloxy, heptyloxy, octyloxy, and isomeric forms thereof; the term "lower-haloalkyl radical" is intended to remain an alkyl radical containing from one to eight carbon atoms, such as methyl, ethyl, propyl, butyl, amyl, hexyl, heptyl, octyl, and isomeric forms thereof, which radical is substituted by one or more atoms of fluorine, chlorine, bromine or iodine; the term "lower-aralkyl radical" is intended to mean an aralkyl radical containing from seven to thirteen carbon atoms such as benzyl, phenethyl, or benzhydryl; the term "lower-aralkoxy" radical is intended to mean an aralkoxy radical containing from seven to thirteen carbon atoms such as benzyloxy, phenethoxy or benzhydryloxy; the term "lower-aryl radical" is intended to mean an aryl radical containing from six to twelve carbon atoms such as phenyl, tolyl, xylyl, naphthyl, or biphenyl; the term "lower-haloaryl radical" is intended to mean an aryl radical containing from six to twelve carbon atoms such as phenyl, tolyl, xylyl, naphthyl or biphenyl, which radical is substituted by one or more atoms of chlorine, bromine, fluorine or iodine.

The process of the invention is carried out advantageously by heating a mixture of the indole starting material (II), the amide having the formula



wherein R₂, R₃, and R₄ have the significance hereinbefore described, and phosphorus oxychloride at a temperature within the range of about fifty to about 150 degrees centigrade for a period of about one to about ten hours. The preferred reaction temperature is within the range of about eighty to about ninety degrees centigrade. Advantageously the reactants are admixed at a temperature of about twenty degrees centigrade or less, external cooling being applied where necessary, and, when the admixture is complete, the temperature of the

reaction mixture is raised to the above-indicated level. Although the reactants can be mixed in any order in the preliminary stage, it is preferred that the phosphorus oxychloride is first added to the amide and that to this mixture is then added the compound having the formula (II) in solution in a further quantity of the amide, the temperature being maintained at or below twenty degrees centigrade throughout the mixing operations.

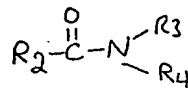
While the relative molecular proportions of the components of the reaction mixture can vary over a wide range, it is advantageous that the phosphorus oxychloride be employed in an amount which is in excess of that which would represent an equimolar amount with respect to the starting indole. The proportion of amide is preferably greatly in excess of that which would represent equimolar proportions with respect to both the phosphorus oxychloride and the indole. The excess of amide serves as a convenient solvent medium for the reaction. If desired, however, and especially where the amide is a solid, there may also be present in the reaction mixture an inert solvent such as dioxan, or tetrahydrofuran.

After the reaction has been completed, the desired indolyl ketone having the formula (I) is isolated from the reaction mixture in a simple and convenient manner by diluting the latter with water, separating excess water-immiscible solvent, if any, basifying the aqueous layer and isolating the so liberated 3-indolyl ketone by conventional procedures, for example, by filtration or by solvent extraction. The product so obtained can be purified by conventional procedures, for example by recrystallization as by distillation under reduced pressure.

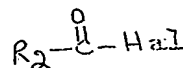
The indoles which are unsubstituted in the 3-position, and which are employed as starting materials in the process of the invention, can be prepared by methods which are well-known in the art. Such methods are summarized in Chemistry of Carbon Compounds, Edited by E. H. Rodd, Vol IV^a, pages 71 to 77, Elsevier, New York, 1957. Indoles which are suitable for use in the process of the invention include the following: indole, 1-methylindole, 1-methyl-2-benzylindole, 1,2-diethylindole, 1-benzylindole, 1-phenethyl-2-phenylindole, 1-methyl-2-phenylindole, 1-ethyl-2-(*p*-chlorophenyl)-5-methylindole, 1-ethyl-2-(*p*-chlorophenyl)-5-methylindole, 1-phenethyl-2-propyl-6-benzylindole, 1-phenethyl-2-propyl-6-benzylindole, 1-hexyl-6-benzylindole, 1-propyl-2-naphthyl-5-methoxyindole, 1-methyl-5-methoxyindole, 1-ethyl-2-phenyl-5-ethoxyindole, 1,2-dibenzyl-5,6-diethoxyindole, 1-phenethyl-2-phenyl-5-chloroindole, 1-ethyl-2-tolyl-5-bromoindole, 1-ethyl-2-phenyl-5-methylindole, 1-benzyl-2,7-diethylindole, 1-phenethyl-2-phenyl-5,6-dimethylindole, 1,5-dimethylindole, 1-benzyl-2,5-diphenylindole, 1-

ethyl-2-(*p*-biphenyl)indole, 1-methyl-2-(*p*-biphenyl)indole, 1-benzyl-2-phenyl-5,7-dichloroindole, 1-phenyl-7-methoxyindole, 2-phenyl-6-methylindole, 2-phenylindole, 4-chloroindole, 2-(*p*-biphenyl)-5,7-dichloroindole, 2-methyl-5,7-dichloroindole, 2-phenyl-4,7-dichloroindole, 5,6-dimethoxyindole, 2-(*p*-tolyl)-5-methylindole 5-bromoindole, 2-methylindole, 5-ethylindole, 7-methylindole, 2,4-dimethylindole, 5-benzylindole, 6-benzylindole, 2-phenyl-5,7-dimethylindole, 2,5-diphenylindole, 5-ethoxyindole, 2,4,7-trimethylindole, 2-benzylindole, 5,6-dibromoindole, 2-methyl-5,6-dimethoxyindole, 2-methyl-5-fluoroindole, 2-hexylindole, 2-(2-naphthyl)-7-chloroindole, 2-*t*-butylindole, 7-benzylindole, 2-*p*-chlorophenyl-5-methylindole, 2-*p*-chlorophenyl-1-ethylindole, 2-*p*-chlorophenyl-1-propylindole, 2-*p*-chlorophenyl-1-isobutylindole, and 2-*p*-chlorophenyl-5,7-dichloroindole.

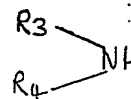
The amides having the formula



which are employed in the process of the invention can be prepared by processes which are well known in the art for the synthesis of amides. For example, the amides can be prepared by the reaction of an acid halide



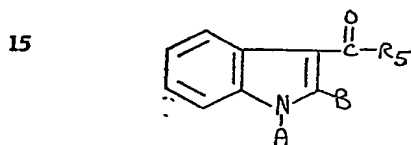
with an amine



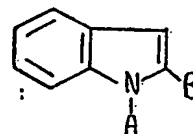
wherein R_2 , R_3 , and R_4 have the significance hereinbefore defined and Hal represents a halogen atom. Amides which are suitable for use in the process of the invention include the following: N-methylacetamide, N,N-dimethylacetamide, N,N-diethylacetamide, N-methylpropionamide, N,N-dimethylchloroacetamide, N,N-dimethylbenzamide, N,N- α,α -pentamethylacetamide, N,N- α -trimethylbutylamide, N,N- β -trimethyl- α -ethylbutylamide, N,N-dimethylisovaleramide, N,N-dimethyldiphenylacetamide, N,N,N',N'-tetramethylmalonamide, N,N-diisobutylacetamide, N,N-di-n-hexylacetamide, N-n-butylacetamide, N-sec-butylacetamide, N,N-di-n-butylacetamide, N-amylacetamide, N-1-methylheptylacetamide and N,N-diethylenanthramide.

While it is possible to employ in the process of the invention, an amide which is unsubstituted on the nitrogen atom, that is to say in which both the radicals R_3 and R_4 are hydrogen atoms, it is preferable to employ an amide which carries at least one lower-alkyl radical as substituent on the nitrogen atom in order to ensure a good yield of the desired compound having the formula (I). The highest yields are obtained using an amide in which the nitrogen atom carries two lower-alkyl radicals.

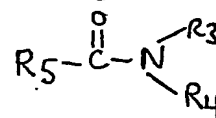
The novel compounds of the invention comprise the compounds having the formula:



wherein A and B represent hydrogen or lower-alkyl radicals, and R_5 represents a branched-chain alkyl group containing from four to eight carbon atoms, inclusive. These compounds can be prepared by the process of the invention using as starting materials an indole having the formula:



and an amide having the formula



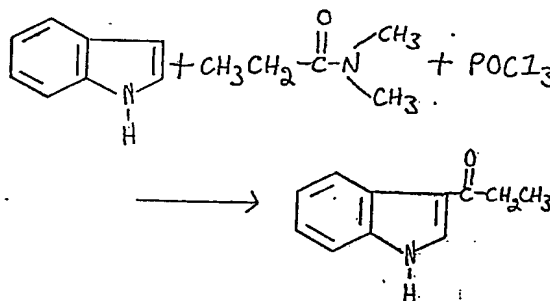
wherein A, B, R_3 , R_4 and R_5 have the significance hereinbefore described.

The novel compounds having the formula (III) above exhibit activity as central nervous system depressants. Illustratively, the compounds 3-indolyl t-butyl ketone, 3-(2-methylindolyl) t-butyl ketone and 3-(2-methylindolyl) 2-methyl-3-pentyl ketone exhibit anticonvulsant activity; the compounds 3-(1-ethyl-2-methylindolyl) iso-butyl ketone and 3-(2-methylindolyl) 2-methyl-3-pentyl ketone depress motor activity.

The novel compounds of the invention can be combined with solid or liquid pharmaceutical carriers and formulated as tablets, powder packets, or capsules, or dissolved or suspended in suitable solvents, for oral or parenteral administration.

The following examples are illustrative of the process and products of the present invention but are not to be construed as limiting.

EXAMPLE 1. 3-propionylindole.



To eighteen milliliters of N,N-dimethylpropionamide cooled to five degrees centigrade was added slowly 11.9 grams (0.077 mole) of phosphorus oxychloride, the temperature being maintained below twenty degrees centigrade throughout. After the addition was complete, the mixture was stirred for a further twenty minutes before a solution of 6.5 grams (0.056 mole) of indole in nine milliliters of N,N-dimethylpropionamide was added slowly, the temperature being maintained below forty degrees centigrade throughout. The resulting mixture was heated to 87 degrees centigrade for

two hours, cooled and diluted with 100 milliliters of ice cold water. The mixture was filtered and the filtrate was treated with a solution of twenty grams of sodium hydroxide in sixty milliliters of water. The solid which separated was collected, washed with water and recrystallized from a mixture of benzene and Skellysolve B (mixture of hexanes). There was obtained 8.3 grams of 3-propionylindole having a melting point of 171 to 173 degrees centigrade, identical with an authentic specimen.

EXAMPLE 2.
3-chloroacetylindole.

Using the procedure described in Example 1, but substituting N,N-dimethylchloroacetamide for N,N-dimethylpropionamide, there was obtained 3-chloroacetylindole in the form of a crystalline solid having a melting point of 233 to 234 degrees centigrade, identical with an authentic specimen.

EXAMPLE 3.
3-acetylindole.

Using the procedure described in Example 1, but substituting N-methylacetamide for N,N-dimethylpropionamide, there was obtained 3-acetylindole in the form of a crystalline solid having a melting point of 191 to 193 degrees centigrade, identical with an authentic specimen.

Anal.: Calcd. for $C_{11}H_{11}NO$: C, 81.42; H, 5.01; N, 6.33
Found: C, 81.35; H, 5.03; N, 6.39.

EXAMPLE 5.
3-acetyl-5-benzyloxyindole.

A quantity of eighteen milliliters of N,N-dimethylacetamide was cooled to five degrees centigrade and seven milliliters (0.075 mole) of phosphorus oxychloride was added slowly, keeping the temperature below twenty degrees centigrade.

When the addition was complete, a solution of 12.5 grams (0.056 mole) of 5-benzyloxyindole and nine milliliters of N,N-dimethylacetamide was added slowly, keeping the temperature below forty degrees centigrade. The mixture was heated to 87 degrees centigrade for two hours and then allowed to cool. The resulting red mass was dissolved in water and extracted with 100 milliliters of ether. The aqueous layer was separated and made alkaline by the addition of aqueous sodium hydroxide solution. The solid which separated was collected, washed with water, refluxed with 100 milliliters of ethanol containing a small amount of charcoal, and the solution filtered. The filtrate was allowed to cool and the solid which separated was collected and dried. A second crop of solid was obtained by concentration of the mother liquor. There was thus obtained 10.5 grams of 3-acetyl-5-benzyloxyindole in the form of a crystalline solid having a melting point of 189 to 190 degrees centigrade, identical with an authentic specimen.

EXAMPLE 6.
2-methyl-3-acetylindole.

Using the procedure described in Example 1, but substituting N,N-dimethylacetamide for N,N-dimethylpropionamide and 2-methylindole for indole, there was obtained 2-methyl-

EXAMPLE 4.
3-benzoylindole.

A mixture of fourteen milliliters (0.15 mole) of phosphorous oxychloride, 36 grams (0.24 mole) of N,N-dimethylbenzamide and thirteen grams (0.112 mole) of indole was heated at 84 degrees centigrade for two hours. The resulting mixture was cooled, treated with 100 milliliters of ice-water and stirred until the gummy mass was broken up. The solid which had separated was then extracted with three portions, each of fifty milliliters, of hot ethanol. The ethanol extracts were combined and allowed to cool. The solid which separated was collected by filtration and dried. There was thus obtained 13.5 grams of 3-benzoylindole in the form of a crystalline solid having a melting point of 241 to 243.5 degrees centigrade.

3-acetylindole in the form of a crystalline solid having a melting point of 195 to 196 degrees centigrade, identical with an authentic specimen.

EXAMPLE 7.
3-(2-methylindolyl) t-butyl ketone.

A quantity of eighteen milliliters of N,N- α,α,α -pentamethylacetamide was cooled to five degrees centigrade and 23.8 grams (0.15 mole) of phosphorus oxychloride was added slowly, the temperature being maintained below ten degrees centigrade throughout. To the solution so obtained was added dropwise a solution of thirteen grams (0.1 mole) of 2-methylindole and eighteen milliliters of N,N- α,α,α -pentamethylacetamide, the temperature being maintained at twenty to 25 degrees centigrade throughout. The resulting mixture was heated at 82 degrees centigrade for two hours, cooled to room temperature and diluted with 200 milliliters of ice-water. The mixture was filtered and the solid so obtained was slurried with a further 200 milliliters of water and again filtered. The combined filtrates were treated with a solution of forty grams of sodium hydroxide in 200 milliliters of water. The oil so liberated was extracted with 100 milliliters of ether and the ethereal extract was dried over anhydrous potassium carbonate. The ether solution was evaporated to dryness and the residual solid was recrystallized twice from a mixture of benzene and petroleum ether. There was thus obtained 10.6 grams of 3-(2-methylindolyl)t-butyl ketone in the form of a red crystalline solid having a melting point of 134 to 135 degrees centigrade after softening at 126 degrees centigrade.

Anal.: Calcd. for $C_{14}H_{17}NO$: C, 78.11; H, 7.94; N, 6.50
Found: C, 78.20; H, 8.53; N, 6.32.

EXAMPLE 8.

3-(2-methylindolyl) sec-butyl ketone.

A quantity of 36 milliliters of N,N,α -trimethylbutyramide was cooled to five degrees centigrade and fourteen milliliters (0.15 mole) of phosphorus oxychloride was added slowly, the temperature being maintained below ten degrees centigrade throughout. To the solution so obtained was added dropwise a solution of thirteen grams (0.1 mole) of 2-methylindole in eighteen milliliters of N,N,α -trimethylbutyramide, the temperature being maintained at twenty to 25 degrees centigrade throughout. The resulting mixture was heated at 82 degrees centigrade for two hours, cooled and poured into 200 milliliters of ice-water. The mixture was made alkaline by the addition of aqueous sodium hydroxide solution and was

extracted with 200 milliliters of ether. The ethereal extract was separated, dried over anhydrous potassium carbonate and evaporated to dryness. The residue was distilled under reduced pressure to remove unchanged N,N,α -trimethylbutyramide (boiling point 47 to 51 degrees centigrade at a pressure of 0.5 millimeter of mercury) and the residue was extracted with petroleum ether. The petroleum ether extract was concentrated to yield a yellow oil which was recrystallized from a mixture of benzene and Skellysolve B and then from aqueous ethanol. There was thus obtained 3.9 grams of 3-(2-methylindolyl) secbutyl ketone in the form of a crystalline solid having a melting point of 101 to 103 degrees centigrade.

Anal.: Calcd. for $C_{14}H_{17}NO$: C, 78.11; H, 7.94; N, 6.50
Found: C, 78.01; H, 8.28; N, 6.28

EXAMPLE 9.

3-(2-methylindolyl) 2-methyl-3-pentyl ketone.

A quantity of 36 milliliters of N,N,β -trimethyl- α -ethylbutyramide was cooled to five degrees centigrade and fourteen milliliters (0.15 mole) of phosphorus oxychloride was added slowly, the temperature being maintained below ten degrees centigrade throughout. To the solution so obtained was added dropwise a solution of thirteen grams (0.1 mole), of 2-methylindole and eighteen milliliters of N,N,β -trimethyl- α -ethylbutyramide, the temperature being maintained at 25 to thirty degrees centigrade throughout. The resulting mixture was heated at 82 degrees centigrade for two hours, cooled and poured into 200 milliliters of ice-water. The acid solution was quickly extracted with 100 milliliters of ether and the aqueous

layer was separated, made alkaline by the addition of aqueous sodium hydroxide solution and extracted with 100 milliliters of ether. The ethereal extract was separated, washed well with water and dried over anhydrous potassium carbonate. The dried solution was mixed with a small quantity of Nuchar 190-N (an activated charcoal), filtered and the filtrate evaporated to dryness. The residue was extracted with 100 milliliters of petroleum ether, the extract was filtered, treated with Nuchar 190-N until very little color remained and concentrated to dryness. The residue was recrystallized twice from aqueous alcohol. There was thus obtained six grams of 3-(2-methylindolyl)-2-methyl-3-pentyl ketone in the form of a crystalline solid having a melting point of 106 to 109 degrees centigrade.

Anal.: Calcd. for $C_{18}H_{21}NO$: C, 78.96; H, 8.69; N, 5.75
Found: C, 78.97; H, 9.11; N, 5.74.

EXAMPLE 10.

3-(2-methylindolyl) isobutyl ketone.

Using the procedure described in Example 8, but substituting N,N -dimethylisovaleramide for N,N,α -trimethylbutyramide, there was

obtained 3-(2-methylindolyl) isobutyl ketone in the form of a crystalline solid having a melting point of 139 to 140 degrees centigrade.

Anal.: Calcd. for $C_{14}H_{17}NO$: C, 78.11; H, 7.94; N, 6.50
Found: C, 78.21; H, 7.85; N, 6.35.

EXAMPLE 11.

3-(1-ethyl-2-methylindolyl) isobutyl ketone.

Using the procedure described in Example 8, but substituting N,N -dimethylisovaleramide for N,N,α -trimethylbutyramide and 1-ethyl-2-methylindole for 2-methylindole, there was ob-

tained 3-(1-ethyl-2-methylindolyl) isobutyl ketone in the form of an oil having a boiling point of 136 to 138 degrees centigrade at a pressure of 0.5 millimeter of mercury; n_D^{20} 1.5780.

Anal.: Calcd. for $C_{16}H_{21}NO$: C, 78.96; H, 8.69; N, 5.75
Found: C, 79.17; H, 8.72; N, 5.89.

EXAMPLE 12.
3-diphenylacetylindole.

A mixture of fourteen milliliters (0.15 mole) of phosphorus oxychloride, forty grams of N,N-dimethyldiphenylacetamide and thirteen grams (0.112 mole) of indole was heated at 82 to 84 degrees centigrade for two hours. The resulting gum was cooled and 200 milliliters of ice-water was added. The mass was poured into 1500 milliliters of water and the aqueous layer was decanted and made alkaline by the addition of aqueous sodium hydroxide solution. The gummy solid which separated was dissolved in fifty milliliters of hot Skellysolve B and the solution was filtered. The filtrate was cooled with solid carbon dioxide and the solid which separated was filtered to yield seven grams of impure starting amide. The filtrate was evaporated to dryness and four grams of the residual oil was placed on a Florisil (magnesium silicate) column (Florisil is a Registered Trade Mark). The column was eluted with six liters of a mixture of five percent acetone, 25 percent benzene and seventy percent Skellysolve B. The eluate was evaporated to dryness. The residue crystallized after drying at 55 degrees centigrade under reduced pressure and was recrystallized twice from benzene and finally from methanol. There was thus obtained two grams of 3-diphenylacetylindole in the form of a crystalline solid having a melting point of 191 to 193 degrees centigrade; the ultra-violet absorption spectrum showed maxima at 303 m μ , 260m μ , 243 m μ and 206 m μ .

Anal.: Calcd. for C₂₂H₁₇NO: N, 4.49
Found: N, 4.73.

EXAMPLE 13.
1-ethyl-3-acetylindole.

Using the procedure described in Example 1, but substituting 1-ethylindole for indole and N,N-dimethylacetamide for N,N-dimethylpropionamide, there was obtained 1-ethyl-3-acetylindole having a melting point of 87 to 89 degrees centigrade.

EXAMPLE 14.

1-ethyl-2-phenyl-3-propionyl-5-ethoxyindole.

Using the procedure described in Example 1, but substituting 1-ethyl-2-phenyl-5-ethoxyindole (J. Chem. Soc. 1944, 670) for indole there was prepared 1-ethyl-2-phenyl-3-propionyl-5-ethoxyindole.

EXAMPLE 15.

3-acetyl-2-phenyl-5-chloroindole.

Using the procedure described in Example 5, but substituting 2-phenyl-5-chloroindole (J. Chem. Soc. 1948, 847) for 5-benzoyloxyindole, there was prepared 3-acetyl-2-phenyl-5-chloroindole.

EXAMPLE 16.

1-ethyl-2-phenyl-3-acetyl-5-methylindole.

Using the procedure described in Example 5, but substituting 1-ethyl-2-phenyl-5-methyl-

indole (J. Chem. Soc. 1943, 58) for 5-benzoyloxyindole, there was prepared 1-ethyl-2-phenyl-3-acetyl-5-methylindole.

EXAMPLE 17.

2,5-diphenyl-3-acetylindole.

Using the procedure described in Example 5, but substituting 2,5-diphenylindole [J. Org. Chem. 2, 235 (1937)] for 5-benzoyloxyindole there was prepared 2,5-diphenyl-3-acetylindole.

EXAMPLE 18.

1-ethyl-2-(p-biphenyl)-3-benzoylindole.

Using the procedure described in Example 4, but substituting 1-ethyl-2-(p-biphenyl)indole (J. Chem. Soc. 1948, 847) for indole there was prepared 1-ethyl-2-(p-biphenyl)-3-benzoylindole.

EXAMPLE 19.

1-benzyl-3-acetylindole.

Using the procedure described in Example 5, but substituting 1-benzylindole [Chem. Ber. 87, 127—9 (1954)] for 5-benzoyloxyindole, there was prepared 1-benzyl-3-acetylindole.

EXAMPLE 20.

2-benzyl-3-acetylindole.

Using the procedure described in Example 5, but substituting 2-benzylindole [J. Chem. Soc. 1954, 2582] for 5-benzoyloxyindole, there was prepared 2-benzyl-3-acetylindole.

EXAMPLE 21.

1-benzyl-3-acetyl-4-bromoindole.

Using the procedure described in Example 5, but substituting 1-benzyl-4-bromoindole [Chem. Ber. 87, 127 (1954)] for 5-benzoyloxyindole, there was prepared 1-benzyl-3-acetyl-4-bromoindole.

EXAMPLE 22.

2-(2,5-xylyl)-3-benzoylindole.

Using the procedure described in Example 4, but substituting 2-(2,5-xylyl)indole [Rec. trav. chim. 68, 441 (1949)] for indole, there was prepared 2-(2,5-xylyl)-3-benzoylindole.

EXAMPLE 23.

2-p-chlorophenyl-3-acetyl-5-methylindole.

Using the procedure described in Example 5, but substituting 2-p-chlorophenyl-5-methylindole (J. Chem. Soc. 1943, 58) for 5-benzoyloxyindole there was prepared 2-p-chlorophenyl-3-acetyl-5-methylindole.

EXAMPLE 24.

2-p-chlorophenyl-3-acetyl-5,7-dichloroindole.

Using the procedure described in Example 5, but substituting 2-p-chlorophenyl-5,7-dichloroindole [J.A.C.S. 70 3421 (1948)] for 5-benzoyloxyindole, there was prepared 2-p-chlorophenyl-3-acetyl-5,7-dichloroindole.

EXAMPLE 25.

3-indolyl n-hexyl ketone.

Using the procedure described in Example 1, but substituting N,N-diethylenanthamide [Rec. trav. chim. 6, 249 (1887)] for N,N-dimethylpropionamide, there was obtained 3-indolyl n-hexyl ketone.

EXAMPLE 26.
3-acetylindole.

Using the procedure described in Example 1, but substituting *N,N*-di-*n*-butylacetamide [J.A.C.S. 59, 1203 (1937)] for *N,N*-dimethylpropionamide, there was obtained 3-acetylindole having a melting point of 191 to 193 degrees centigrade identical with the product obtained in Example 3.

Anal.: Calcd. for $C_{11}H_{11}NO$: C, 77.57; H, 7.51; N, 6.96
Found: C, 77.45; H, 7.33; N, 7.20.

EXAMPLE 28.

5-methyl-3-indolyl *t*-butyl ketone.
Using the procedure described in Example 7, but substituting 5-methylindole (J. Chem. Soc. 1949, Suppl. Issue, No. 1, 5231) for 2-methylindole, there was obtained 5-methyl-3-indolyl *t*-butyl ketone.

EXAMPLE 29.

5-chloro-3-indolyl *t*-butyl ketone.
Using the procedure described in Example 7, but substituting 5-chloroindole [Ann. 583, 150 (1953)] for 2-methylindole, there was obtained 5-chloro-3-indolyl *t*-butyl ketone.

EXAMPLE 30.

5-fluoro-3-indolyl *t*-butyl ketone.
Using the procedure described in Example 7, but substituting 5-fluoroindole (J. Chem. Soc. 1955, 1283) for 2-methylindole, there was obtained 5-fluoro-3-indolyl *t*-butyl ketone.

EXAMPLE 31.

6-methoxy-3-indolyl *t*-butyl ketone.
Using the procedure described in Example 7, but substituting 6-methoxyindole (J. Chem. Soc. 1938, 97) for 2-methylindole, there was obtained 6-methoxy-3-indolyl *t*-butyl ketone.

EXAMPLE 32.

5-hydroxy-3-indolyl *t*-butyl ketone.
Using the procedure described in Example 7, but substituting 5-benzyloxyindole (J. Chem. Soc. 1937, 1726) for 2-methylindole, there was obtained 5-benzyloxy-3-indolyl *t*-butyl ketone. The latter compound was subjected to hydrogenolysis in alcohol solution using a palladium-on-charcoal catalyst, according to the procedure described in British Specification No. 744,774, to obtain 5-hydroxy-3-indolyl *t*-butyl ketone.

WHAT WE CLAIM IS:—

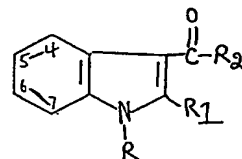
1. A process for the preparation of a 3-indolyl ketone which comprises reacting an indole unsubstituted in the 3-position with phosphorus oxychloride and a carboxylic acid amide of a hydrocarbon carboxylic acid or a hydrocarbon carboxylic acid substituted by one or more inert radicals and a lower-alkylamine.

2. In a process for the preparation of an indolyl ketone having the general formula:

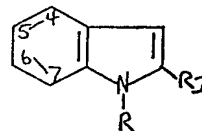
EXAMPLE 27.

3-indolyl *t*-butyl ketone.

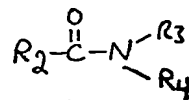
Using the procedure described in Example 7, but substituting indole for 2-methylindole, there was obtained 3-indolyl *t*-butyl ketone in the form of a crystalline solid having a melting point of 159 to 161 degrees centigrade.



wherein R represents hydrogen or a lower-alkyl or lower-aralkyl radical, R_1 represents a hydrogen, lower-alkyl, lower-aralkyl, lower-aryl, or lower-haloaryl radical, R_2 represents lower-alkyl, lower-haloalkyl, lower-aralkyl or lower-aryl radical, and the 4-, 5-, 6- and 7-positions in the benzene nucleus can be substituted by lower-alkyl, lower-aryl, lower-alkoxy, lower-aralkyl, lower-aralkoxy or lower-aryloxy radicals or a halogen, the step of reacting an indole having the general formula:



wherein R and R_1 have the significance hereinbefore defined and the 4-, 5-, 6- and 7-positions in the benzene nucleus can be substituted as hereinbefore described, with phosphorus oxychloride and an amide having the formula

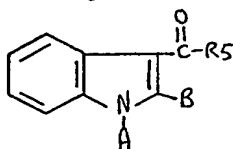


wherein R_2 has the significance hereinbefore defined, R_3 is hydrogen or a lower-alkyl radical, and R_4 represents a lower-alkyl radical.

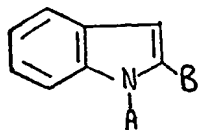
3. The process of claim 2 in which the phosphorus oxychloride and a portion of the amide are admixed at a temperature not substantially greater than twenty degrees centigrade, the mixture so obtained is treated at a temperature not substantially greater than twenty degrees centigrade with a solution of the indole starting material in solution in a

further quantity of the amide, and the resulting mixture is heated at a temperature within the range of about fifty to about 150 degrees centigrade for a period of from about one to about ten hours.

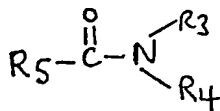
- 5 4. In a process for the preparation of an indolyl ketone having the formula:



- 10 wherein A and B represent hydrogen or lower-alkyl radicals, and R_5 represents a branched-chain alkyl group containing from four to eight carbon atoms, inclusive, the step of reacting in indole having the formula:

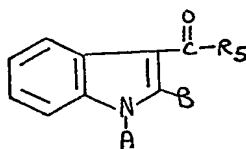


- 15 wherein A and B have the significance hereinbefore defined with phosphorus oxychloride and an amide having the formula



wherein R_3 is hydrogen or a lower-alkyl radical, R_4 represents a lower-alkyl radical and R_5 has the significance hereinbefore defined.

5. A compound having the formula:



wherein A and B represent hydrogen or lower-alkyl radicals, and R_5 represents a branched-chain alkyl group containing from four to eight carbon atoms, inclusive.

- 25 6. 3-indolyl *t*-butyl ketone.
7. 3-(2-methylindolyl) *t*-butyl ketone.
8. 3-(2-methylindolyl) 2-methyl-3-pentyl ketone.
9. 3-(1-ethyl-2-methylindolyl) isobutyl ketone.
10. 3-(2-Methylindolyl) *sec*-butyl ketone.
11. 3-(2-Methylindolyl) isobutyl ketone.
12. A process for the preparation of 3-indolyl ketones substantially as herein described with reference to any of the Examples.
13. 3-Indolyl ketones when prepared by a process as claimed in any of Claims 1 to 4 or 12.

For the Applicants:—
GILL, JENNINGS & EVERY,
Chartered Patent Agents,
51/52, Chancery Lane, London, W.C.2.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☒ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.